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(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : TAYLOR, Anthony, James [GB/GB]; BURNELL, Patricia, Kwong, Phieu [GB/GB]; Glaxo Group Research Limited, Park Road, Ware, Hertfordshire SG12 0DG (GB).

(74) Agents: FILLER, Wendy, Anne et al.; Glaxo Holdings plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

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(54) Title: AEROSOL CONTAINING MEDICAMENTS

(57) Abstract

Aerosol formulations comprising: (A) a medicament selected from the group comprising salmeterol, fluticasone esters, 4-amino-3,5-dichloro-α-[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl] benzenemethanol and physiologically acceptable salts and solvates thereof in particulate form and having a surface coating of a surfactant; and (B) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant; and methods for their preparation.

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Aerosol containing medicaments.

This invention relates to aerosol formulations of use in the administration of medicaments by inhalation.

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a solvent, such as ethanol.

The most commonly used aerosol propellants for medicaments have been Freon 11 (CCl_3F) in admixture with Freon 12 (CCl_2F_2) and Freon 114 ($CF_2Cl.CF_2Cl$). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrogen-containing chlorofluorocarbons and fluorocarbons; medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777. EP 0372777 requires the use of 1,1,1,2-tetrafluoroethane in combination with both a cosolvent having greater polarity than 1,1,1,2-tetrafluoroethane (e.g. an alcohol or a lower alkane) and a surfactant in order to achieve a stable formulation of a medicament powder. In particular it is noted in the specification at page 3, line 7 that "it has been found that the use of Propellant 134a (1,1,1,2-tetrafluoroethane) and drug as a binary mixture or in combination with a conventional surfactant such as sorbitan trioleate does not provide formulations having suitable properties for use with pressurised inhalers".

We have now surprisingly found that, in contradistinction to this teaching, it is in fact possible to obtain stable dispersions of certain finely-powdered medicaments together with certain surfactants in hydrogen-containing fluorocarbon or chlorofluorocarbon propellants such as 1,1,1,2-tetrafluoroethane if the surfactant is present as a dry coating on the particles of medicament. More particularly, such stable dispersions may be

formed where the medicament is selected from salmeterol, fluticasone esters, 4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol, and physiologically acceptable salts and solvates thereof. This is in contrast to the procedure of EP 0372777, where the medicament and surfactant are simultaneously homogenised, e.g. in ethanol, prior to addition of the propellant.

There is thus provided an aerosol formulation comprising (A) a medicament selected from the group comprising salmeterol, fluticasone esters, 4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol, and physiologically acceptable salts and solvates thereof in particulate form and having a surface-coating of a surfactant; and (B) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant.

The propellants for use in the invention may be any hydrogen-containing fluorocarbon or chlorofluorocarbon or mixtures thereof having a sufficient vapour pressure to render them effective as propellants. Such propellants include for example C_{1-4}hydrogen-containing fluorocarbons and chlorofluorocarbons such as CH_2ClF, $CClF_2$-$CHClF$, CF_3-$CHClF$, CHF_2-$CClF_2$, $CHClF$-CHF_2, CF_3-CH_2Cl, CHF_2-CHF_2, CF_3-CH_2F, $CClF_2$-CH_3, CHF_2-CH_3 and CF_3CHFCF_3.

Where mixtures of the hydrogen-containing fluorocarbons or chlorofluorocarbons are employed they may be mixtures of the above identified compounds or mixtures, preferably binary mixtures, with other hydrogen-containing fluorocarbons or chlorofluorocarbons for example $CHClF_2$, CH_2F_2 and CF_3CH_3.

The propellant may additionally contain a volatile saturated hydrocarbon for example n-butane, isobutane, pentane and isopentane. Preferably a single hydrogen-containing fluorocarbon or chlorofluorocarbon is employed as the propellant. Preferably the propellant will be a non-solvent for the medicament. Particularly preferred as propellants are 1,1,1,2-tetrafluoroethane ($CF_3.CH_2F$) and 1,1,1,2,3,3,3-heptafluoro-n-propane ($CF_3.CHF.CF_3$).

It is desirable that the formulations of the invention contain no components which may provoke the degradation of stratospheric ozone. In particular it is desirable that the formulations are substantially free of chlorofluorocarbons such as CCl_3F, CCl_2F_2 and CF_3CCl_3.

It is further desirable that the formulations of the invention are substantially free of liquid components of higher polarity than the propellant employed. In particular formulations which are free of alcohols such as ethanol are preferable.

Polarity may be determined for example, by the method described in European Patent Application Publication No. 0327777.

As used herein "substantially free" means less than 1% w/w based upon the hydrogen-containing fluorocarbon or chlorofluorocarbon, in particular less than 0.5% for example 0.1% or less.

Where appropriate the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

For use in the formulations of the present invention, salmeterol will preferably be in the form of its 1-hydroxy-2-naphthoate salt, the fluticasone ester will preferably be the propionate, and 4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol will preferably be in the form of the (R) enantiomer.

The surfactants for use in the invention will have no affinity for the propellant (that is to say they will contain no groups which have affinity with the propellant).

The surfactants must be physiologically acceptable upon administration by inhalation. Surfactants within this category include materials such as benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate (Span ^{R} 85).

The use of substantially non-ionic surfactants which have reasonable solubility in substantially non-polar solvents is frequently advantageous since it facilitates coating of the medicament particles using solutions of surfactant in non-polar solvents in which the medicament has limited or minimal solubility.

Thus according to a further aspect of the invention the surfactant-coated medicament may be prepared by slurrying particulate (e.g. micronised) medicament with a solution of a surfactant such as lecithin in a substantially non-polar solvent

(e.g. a lower alkane such as isopentane or a chlorofluorocarbon such as trichlorofluoromethane), optionally homogenising the slurry (e.g. by sonication), removing the solvent and if necessary simultaneously and/or subsequently breaking up the resulting solid cake. The thus-obtained surfactant-coated particulate medicaments are novel and form a further feature of the invention.

The formulations of the invention may be prepared by dispersing the surface-coated medicament, obtained as described above, in the chosen propellant in an appropriate aerosol container, e.g. with the aid of sonication.

The particle size of the finely-powdered medicament should be such as to permit inhalation of substantially all of the medicament into the bronchial system upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and preferably in the range 2-10 microns, e.g. 2-5 microns.

The amount of surfactant employed in coating the particulate medicament is desirably in the range 0.01 - 10.0% w/w, preferably 0.05 - 5.0% w/w, relative to the medicament, and may advantageously be chosen such that a substantially monomolecular coating of surfactant is formed. The final aerosol formulation desirably contains 0.005 - 5.0% w/w, preferably 0.01 - 1.0% w/w, of coated medicament relative to the total weight of the formulation.

The following non-limitative Examples serve to illustrate the invention.

EXAMPLE 1

(A) Preparation of Lecithin-coated Salmeterol Hydroxynaphthoate

(a) Lecithin (Epikuron 145V - 3.65mg) was dissolved in a small amount of isopentane and the resulting solution was added to micronised salmeterol hydroxynaphthoate (0.5g). Further isopentane (7.0g total) was added to form a slurry, which was sonicated for 3 minutes. The resulting suspension was dried by evaporating the isopentane at ambient temperature in a fume cupboard, whereafter the resulting dried plug was roughly broken up and then dried further in a vacuum oven. The thus-obtained product was further broken up

using a mortar and pestle to yield lecithin-coated salmeterol hydroxynaphthoate containing 0.73% w/w of lecithin relative to the salmeterol hydroxynaphthoate.

(b) The above procedure was repeated except that 6.10mg of lecithin was employed, whereby a coated product containing 1.22% w/w of lecithin relative to the salmeterol hydroxynaphthoate was obtained.

(c) The above procedure was again repeated except that 7.80mg of lecithin was employed, thereby yielding a coated product containing 1.56% w/w of lecithin relative to the salmeterol hydroxynaphthoate.

(B) Formulation of Lecithin-coated Salmeterol Hydroxynaphthoate in 1,1,1,2-Tetrafluoroethane

Samples of each of the products of Example 1A (a)-(c) (9.1mg) were weighed into aerosol cans. 1,1,1,2-Tetrafluoroethane (18.2g - 99.5% w/w of total fill weight) was added to each can, whereafter suitable metering valves were crimped onto the cans, which were then each sonicated for 5 minutes. The resulting aerosols contained salmeterol in an amount equivalent to 240 actuations at 25µg per actuation.

Example 2

(A) Preparation of lecithin-coated fluticasone propionate

Lecithin (Epikuron 145V - 2.5mg) was dissolved in a small amount of isopentane and the resulting solution was added to micronised fluticasone propionate (0.5g). Further isopentane (20ml) was added to form a slurry, which was sonicated for 3 minutes. The resulting suspension was dried by evaporating the isopentane at ambient temperature in a fume cupboard, whereafter the resulting dried plug was roughly broken up and then dried further in a vacuum oven. The thus-obtained product was further broken up using a mortar and pestle to yield lecithin-coated fluticasone propionate containing 0.5% $^{w}/_{w}$ of lecithin relative to the fluticasone propionate.

(B) Formulation of lecithin-coated fluticasone propionate in 1,1,1,2-tetrafluoroethane

A sample of the product of Example 2(A) (9.1mg) was weighed into aerosol cans, 1,1,1,2-Tetrafluoroethane (18.2g - 99.5% w/w of total fill weight) was added to each can, whereafter suitable metering valves were crimped onto the cans, which were then each sonicated for 5 minutes. The resulting aerosols contained fluticasone propionate in an amount equivalent to 240 actuations at 25μg per actuation.

Example 3

(A) Preparation of Oleic Acid-coated Salmeterol Hydroxynaphthoate

Oleic acid (10mg) was dissolved in a small amount of isopentane and the resulting solution was added to micronised salmeterol hydroxynaphthoate (1.0g). Further isopentane (25ml total) was added to form a slurry, which was sonicated for 3 minutes. The resulting suspension was dried by evaporating the isopentane at ambient temperature in a fume cupboard, whereafter the resulting dried plug was roughly broken up and then dried further in a vacuum oven. The thus-obtained product was further broken up using a mortar and pestle to yield oleic acid-coated salmeterol hydroxynaphthoate containing 1.0% w/w of oleic acid relative to the salmeterol hydroxynaphthoate.

(B) Formulation of Oleic acid-coated Salmeterol Hydroxynaphthoate in 1,1,1,2-Tetrafluoroethane

Samples of the product of Example 3A (9.1mg) were weighed into aerosol cans. 1,1,1,2-Tetrafluoroethane (18.2g - 99.5% w/w of total fill weight) was added to each can, whereafter suitable metering valves were crimped onto the cans, which were then each sonicated for 5 minutes. The resulting aerosols contained salmeterol in an amount equivalent to 240 actuations at 25μg per actuation.

Example 4

(A) Preparation of Sorbitan Trioleate-coated Salmeterol Hydroxynaphthoate

Sorbitan trioleate (Span 85-10mg) was dissolved in a small amount of isopentane and the resulting solution was added to micronised salmeterol hydroxynaphthoate (1.0g). Further isopentane (25ml total) was added to form a slurry, which was sonicated for 3 minutes. The resulting suspension was dried by evaporating the isopentane at ambient temperature in a fume cupboard, whereafter the resulting dried plug was roughly broken up and then dried further in a vacuum oven. The thus-obtained product was further broken up using a mortar and pestle to yield sorbitan trioleate-coated salmeterol hydroxynaphthoate containing 1.0% w/w of sorbitan trioleate relative to the salmeterol hydroxynaphthoate.

(B) Formulation of Sorbitan Trioleate-coated Salmeterol Hydroxynaphthoate in 1,1,1,2-Tetrafluoroethane

Samples of the product of Example 4A (9.1mg) were weighed into aerosol cans. 1,1,1,2-Tetrafluoroethane (18.2g - 99.5% w/w of total fill weight) was added to each can, whereafter suitable metering valves were crimped onto the cans, which were then each sonicated for 5 minutes. The resulting aerosols contained salmeterol in an amount equivalent to 240 actuations at 25µg per actuation.

Claims

1. An aerosol formulation comprising :

(A) a medicament selected from the group comprising salmeterol, fluticasone esters, 4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl] benzenemethanol and physiologically acceptable salts and solvates thereof in particulate form and having a surface coating of a surfactant; and

(B) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant.

2. A formulation as claimed in Claim 1 wherein the propellant comprises 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.

3. A formulation as claimed in Claim 1 wherein the propellant comprises 1,1,1,2-tetrafluoroethane.

4. A formulation as claimed in any one of Claims 1 to 3 which is substantially free of chlorofluorocarbons.

5. A formulation as claimed in any one of Claims 1 to 4 which is substantially free of liquid components of higher polarity than the propellant.

6. A formulation as claimed in any one of Claims 1 to 5 wherein the coated medicament has a particle size of less than 100 microns.

7. A formulation as claimed in any one of Claims 1 to 6 wherein the surfactant is present in an amount of from 0.01 to 10% w/w based on the medicament.

8. A formulation as claimed in any one of Claims 1 to 7 wherein the surfactant is selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate.

9. A formulation as claimed in any one of Claims 1 to 8 wherein the surfactant-coated medicament is present in an amount of 0.005-5% w/w based upon the total weight of the medicament.

10. A formulation as claimed in any one of Claims 1 to 9 wherein the medicament is salmeterol in the form of its 1-hydroxy-2-naphthoate salt.

11. A formulation as claimed in any one of Claims 1 to 9 wherein the medicament is fluticasone propionate.

12. A formulation as claimed in any one of Claims 1 to 9 wherein the medicament is the (R) enantiomer of 4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino] methyl]benzenemethanol.

13. A method for the preparation of an aerosol formulation comprising dispersing a surface-coated medicament selected from the group comprising salmeterol, fluticasone esters, 4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl] benzenemethanol and physiologically acceptable salts and solvates thereof in a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant in an aerosol container.

14. A method as claimed in Claim 13 wherein the surface-coated medicament is obtained by slurrying particulate medicament with a solution of a surfactant in a substantially non-polar solvent and then removing the solvent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01961

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 9/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	WO, A1, 9111173 (FISONS PLC) 8 August 1991, see the whole document	1-14
P,X	WO, A1, 9111495 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH) 8 August 1991, see the whole document	1-14
A	EP, A2, 0372777 (RIKER LABORATORIES, INC) 13 June 1990, see the whole document	1-14

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
6th March 1992	18. 03. 92
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Maria Peis Maria Peis

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/01961

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9111173	08/08/91	NONE	
WO-A1- 9111495	08/08/91	AU-D- 7211391	21/08/91
		DE-A- 4003272	08/08/91
EP-A2- 0372777	13/06/90	AU-D- 4595689	14/06/90
		CA-A- 2004598	06/06/90
		JP-A- 2200627	08/08/90

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